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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,234	JOHANSEN ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-12 and 15-32* is/are pending in the application.

4a) Of the above claim(s) *18-21 and 26-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12,15-17 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed November 7, 2006 amending claims 1, 4, 17-19 and 22-29 and canceling claims 3, 13 and 14 has been entered.

Claims 1, 2, 4-12 and 15-32 are pending. Claims 18-21 and 26-32 have been previously withdrawn.

Claim Objections

Claims 15-17 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 15-17 depend from claim 1. Claim recites "a bacterial, yeast or fungal cell comprising ... recombinant POI". Therefore, said cell is a cell transformed with a nucleic acid encoding POI using recombinant DNA techniques as required by claims 15-17.

Claim 23 is objected to because it recites "the amino acid sequence set out in SEQ ID No 22" where SEQ ID NO:23 is intended (SEQ ID NO:22 is a nucleotide sequence).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-12, 15-17 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, with dependent claims 2, 4-12, 15-17, 22-25, has been amended to encompass methods comprising "(b) releasing the recombinant POI from the cell by contacting the cell with a membrane extracting composition ... for between 4 to 48 hours" (emphasis added). Applicant indicates that support for this amendment can be found in Example 8, Table 7 (Remarks, page 7). While the table may provide support for said time limitation for releasing *Chondrus crispus* HOX from the yeast *Hansenula polymorpha* HOX using CTAB, the examiner is unable to locate adequate support in the specification for this limitation for any POI using any quarternary ammonium compound. Thus there is no indication that methods comprising such time limitation for any POI were within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 1, 2, 4-12, 15-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, with dependent claims 2, 4-12, 15-17, 22-25, is drawn to a method for releasing any intracellular recombinant protein of interest (POI) using a membrane extracting composition comprising a quarternary ammonium resulting in recombinant POI having a specific activity higher than when it has been extracted by mechanical means. Therefore, the claims are drawn to a method of making of a genus of POIs. Said genus encompasses unlimited number of species having wildly different structures and functions. The specification and claims do not indicate what distinguishing attributes shared by the members of the genus. Structural features that could distinguish compounds in the genus from others in the protein classes are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance, is needed. The art teaches that the high level production and purity of a protein depend on the protein and its source whether said source is a naturally-occurring or recombinant cell. The art of protein purification in general is highly developed. However, the development of an appropriate purification scheme for a specific protein with known characteristics requires additional trial and error experimentation. Claim 1 further recites a wide range of quarternary ammonium concentrations (0.05%-6.0%) and time (4-48 hours). Such

ranges encompass a great number of combinations of concentration and time plus other parameters such as temperature and pH, for example. The specification dies not provide a correlation between the specific POI and said parameters that are common to all members of the POI genus. Claims 3-12 recite specific extracting compositions, specific temperatures and pH optimum. The specification discloses the production of *Chondrus crispus* HOX in the yeasts *Hansenula polymorpha* and *Pichia pastoris* using an engineered DNA of SEQ ID NO:22 that accommodates yeasts codon preferences. The extraction of thus expressed HOX was carried out using specific quarternary ammonium salts as an extracting agent under specific conditions that were empirically found.

Claim 22 is limited to POI that is HOX (hexose oxidase). The genus of HOXs encompasses any HOX from any source. The specification teaches a single representative species of HOXs, *Chondrus crispus* HOX having the amino acid sequence of SEQ ID NO:23. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being HOX. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

With regard to a process, the single representative is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed tremendously diverse genus. Therefore, one skilled in the art cannot

reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 1, 2, 4-12, 15-17 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for releasing recombinant HOX having the amino acid sequence of SEQ ID NO:23 under specific conditions comprising concentration, time, temperature and pH range, does not reasonably provide enablement for a method for releasing of any POI using any quarternary ammonium at concentrations 0.05%-6.0% within 4 to 48 hours at undefined pH and temperature. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for releasing recombinant POI using a quarternary ammonium at concentrations 0.05%-6.0% within 4 to 48 hours. The ranges are significantly wide being more than one order of magnitude. There is no guidance in

the specification as to what are other essential conditions such as temperature and pH, for example, and how the combined experimental conditions change depending on the structure of the POI. The art teaches solubilization of recombinant proteins using a quarternary ammonium compounds such as CTAC, CTAB, LTAB, etc. In every such case finding the right combination of experimental conditions requires trial and error experimentation.

The specification discloses the production of *Chondrus crispus* HOX in the yeasts *Hansenula polymorpha* and *Pichia pastoris* using an engineered DNA of SEQ ID NO:22 that accommodates yeasts codon preferences. The extraction of thus expressed HOX was carried out using specific quarternary ammonium salts as an extracting agent under specific conditions that were empirically found. It is noted that using said codon preferred DNA for expression in a bacterial or fungal cell will not be beneficial.

Furthermore, the specification does not support the broad scope of the claims which encompasses HOX having an undefined identity to SEQ ID NO: 23 because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting a HOX activity; (B) the general tolerance of HOX to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any HOX residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

While recombinant hybridization techniques are known, only highly homologous sequences can be identified using a given sequence. The state of the art provides no

reasonable expectation of success in obtaining HOX encoded by a DNA encoding SEQ ID NO:23 having an unknown identity to SEQ ID NO: 22 and the result of such screening is unpredictable.

Without sufficient guidance, beyond that provided, releasing a recombinant POI other than HOX encoded by SEQ ID NO:22 within the range of specific conditions is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-12, 15-17 and 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, with dependent claims 2, 4-12, 15-17, 22-25, is drawn to "A method for releasing a soluble or membrane associated intracellular recombinant protein of interest (POI) form a bacterial, yeast or fungal cell". It appears that characteristics such as "soluble or membrane associated" relate to a native protein and not to said protein obtained by recombinant techniques. Furthermore, POI "from a bacterial, yeast or fungal cell" is confusing. It is unclear whether the protein should be bacterial, yeast or fungal protein or it can be any protein that is expressed in said cell. Amending the claim

to recite "releasing POI from a bacterial, yeast or fungal cell transformed with a DNA encoding said POI", for example, is suggested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-12 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Puri et al.

Puri et al (The Biochem. Journal (August 1, 1992) Vol. 285, pages 871-879) teach the method for solubilization of recombinant proteins expressed in *E. coli* using CTAC (0.5-5%, 1 hour, ambient temperatures, specifically 55^{O}C) (page 872). They further teach that solubilization improves with temperature from 20^{O}C to 50^{O}C (page 878, 1st column, last paragraph). They further teach that "at low concentrations [of CTAC] the time for maximal solubilization is impractical" (emphasis added, sentence bridging columns 1-2 of page 878). Therefore, Puri et al teachings confirm that experimental trial requires for solubilization of each recombinant protein. They teach that concentration of CTAC and time is chosen depending on many factors including the time available.

It would have been obvious to one of ordinary skill in the rat at the time the invention was made to try various combinations of CTAC concentrations and incubation

time and choose the most suitable in view of various considerations. One of ordinary skill in the art would be motivated to try several experimental conditions in order to find the most suitable. One of ordinary skill in the art would have a reasonable expectation that at concentrations lower than 0.5% CTAC the incubation time should be increased beyond 1 hour as taught by Puri et al.

Response to Arguments

Applicant's arguments filed November 7, 2006 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph rejections, Applicant argues that "the present application provides general guidelines as to the quarternary ammonium compounds to be used, including the concentrations levels that are most effective, as well as guidelines as to the appropriate pH, temperature, and incubation times" (Remarks, page 9, 1st full paragraph). applicant further argues that "as amended herein the claims now require that the protein of interest be a recombinant protein, and that the protein be from a bacterial, yeast or fungal cell, thereby providing further identifying characteristics of these proteins which may be extracted by the claimed methods" (page 10, penultimate paragraph). this is not [persuasive because the protein whether it obtained by recombinant or any other techniques is the same and therefore, citation of "a bacterial, yeast or fungal cell" adds nothing to identifying characteristics of the protein itself. Further, "Applicants respectfully submit that the process as claimed is general in nature, and may be applied to a number of proteins with modifications that are

commonplace to those of skill in the art (page 10, last sentence). This is not found persuasive because a general guidance of the claimed method such as solubilization of recombinant proteins is known in the art. it is expected that the precise experimental conditions would vary depending on the given POI. However, claimed method encompasses wide range of conditions that do not decrease the time needed to find the precise conditions in each case. If the claimed method introduces the improvement relative to a general guidelines, there is no showing of unexpected results.

With regard to the 112, 2nd paragraph rejection, applicant argues that "Specific activity is well understood in the art as a measure of the enzyme activity per unit mass of enzyme" (page 12). It is noted that POI is not limited to an enzyme ands each may have different and various activities.

The 102(b) rejection over Sundhey is withdrawn in view of the amendment.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

January 24, 2007